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A Pilot Trial of Recombinant Desulfatohirudin Compared With Heparin in Conjunction With Tissue-Type Plasminogen Activator and Aspirin for Acute Myocardial Infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) 5 Trial

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Objectives. **The purpose of this study was to assess the value of recombinant desulfatohirudin (hirudin) as adjunctive therapy to thrombolysis in acute myocardial infarction.**

Background. **Failure to achieve initial reperfusion and reocclusion of the infarct-related artery remain major limitations of thrombolytic therapy despite aggressive regimens of heparin and aspirin. Hirudin, a direct thrombin inhibitor, has been shown in experimental models to enhance thrombolysis and reduce reocclusion.**

Methods. **The Thrombolysis in Myocardial Infarction (TIMI) 5 trial was a randomized, dose-ranging, pilot trial of hirudin versus heparin, given with front-loaded tissue-type plasminogen activator and aspirin to 246 patients with acute myocardial infarction. Patients received either intravenous heparin or hirudin at one of four ascending doses for 5 days. Patients underwent coronary angiography at 90 min and at 18 to 36 h, unless rescue angioplasty was performed.**

Results. **The primary end point, TIMI grade 3 flow in the infarct-related artery at 90 min and 18 to 36 h without death or reinfarction before the 18- to 36-h catheterization was achieved in 97 (61.8%) of 157 evaluable hirudin-treated patients compared with 39 (49.4%) of 79 evaluable heparin-treated patients ($p = 0.07$). All four doses of hirudin led to similar findings in the angiographic and clinical end points. At 90 min, TIMI grade 3 flow was present in 105 (64.8%) of 162 hirudin-treated patients compared with 48 (57.1%) of 84 heparin-treated patients (p = NS). Infarct-related artery patency (TIMI grade 2 or 3 flow) was similar in the two groups (82.1% and 78.6%, respectively). At 18 to 36 h, 129 (97.8%) of 132 hirudin-treated patients had a patent infarct-related artery compared with 58 (89.2%) of 65 heparin-treated patients ($p = 0.01$). Reocclusion by 18 to 36 h occurred in 2 (1.6%) of 123 hirudin-treated patients versus 4 (6.7%) of 60 heparin-treated patients ($p = 0.07$). Death or reinfarction occurred during the hospital period in 11 (6.8%) of 162 hirudin-treated patients compared with 14 (16.7%) of 84 heparin-treated patients ($p = 0.02$). Major spontaneous hemorrhage occurred in 1.2% of hirudin-treated patients versus 4.7% of heparin-treated patients ($p = 0.09$), and major hemorrhage at an instrumented site occurred in 16.3% and 18.6%, respectively (p = NS).**

Conclusions. **Hirudin is a promising agent compared with heparin as adjunctive therapy with thrombolysis for acute myocardial infarction, and its evaluation in larger trials is warranted.**

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Although thrombolytic therapy has proved to be a major advance in the treatment of patients with acute myocardial infarction, current regimens are limited by failure of initial reperfusion, inadequate perfusion with Thrombolysis in Myocardial Infarction trial (TIMI) grade 2 flow, reocclusion and reinfarction in a significant percent of patients (1,2). Because these problems are associated with increased subsequent mortality (3–6), and because thrombin is thought to play the central role in failed reperfusion, reocclusion and reinfarction (7), there is increased interest in the development of antithrombotic therapies, including direct thrombin inhibitors, that have shown promise in experimental studies (8–11).

Hirudin is the naturally occurring anticoagulant derived from the leech *Hirudo medicinalis* (12). Recombinant desulfatohirudin (CGP 39393) is a 65-amino acid polypeptide identical to natural hirudin except for a missing sulfate group on the tyrosine 63 (13) (and is referred to as hirudin herein). Hirudin selectively binds to thrombin in a 1:1 stoichiometric relation at two sites: 1) The amino terminus of hirudin binds to the active catalytic site of thrombin; and 2) the carboxy terminus of hirudin binds to the "anion-binding exosite" of thrombin (the site where thrombin binds to fibrinogen or platelets) (13,14). As an essentially irreversible inhibitor, hirudin inhibits all of the major actions of thrombin, including the cleavage of fibrinogen to fibrin, the activation of platelets and the activation of thrombin's own positive amplification reactions (12,13). In animal models hirudin is superior to heparin in decreasing platelet deposition and thrombus formation (15), and in models of coronary thrombosis, hirudin has been shown to both speed thrombolysis and decrease reocclusion (9,11).

The TIMI 5 trial was a pilot trial designed to evaluate, in patients with evolving acute myocardial infarction, the safety and effects of hirudin compared with intravenous heparin as adjunctive therapy to tissue-type plasminogen activator (t-PA) and aspirin.

Methods

Eligibility criteria. Patients between the ages of 21 and 75 years were screened for enrollment at 14 clinical centers (see Appendix). To be eligible for study participation patients had to experience ischemic pain lasting at least 30 min, with associated ST segment elevation ≥0.1 mV in at least two contiguous electrocardiographic (ECG) leads or with new left bundle branch block. The onset of pain had to occur within 6 h of planned treatment initiation.

Exclusion criteria were acute pulmonary edema or cardiogenic shock; previous coronary bypass grafting or valve replacement; cardiac catheterization or angioplasty within the previous 2 weeks; thrombolytic therapy for acute myocardial infarction within the previous 2 weeks; current therapeutic anticoagulation; previously documented left bundle branch block; woman of childbearing potential; probable pericarditis; renal dysfunction (creatinine >1.5 mg/dl);

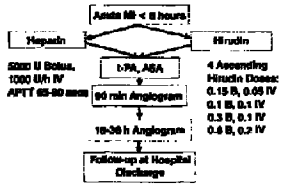

Figure 1. Thrombolysis in Myocardial Infarction 5 study design. APTT = activated partial thromboplastin time; ASA = aspirin; B = bolus (mg/kg [hirudin]); IV = intravenous infusion (mg/kg per h [hirudin]); MI = myocardial infarction; t-PA = tissue plasminogen activator.

other serious illness; hypersensitivity to heparin, aspirin, t-PA or other severe allergies; treatment with another investigational drug within 30 days; history of noncompliance; agitation such that informed consent could not be obtained; previous participation in TIMI 5; and contraindications to thrombolytic therapy. The latter included a past or present bleeding disorder; gastrointestinal or pulmonary bleeding within the previous 12 months; history of cerebrovascular disease at any time, including any form of stroke or transient ischemic attack; history of intraocular bleeding, including retinal hemorrhage; a reliably obtained blood pressure >180/100 mm Hg; significant surgical procedure or severe trauma within 6 months; cardiopulmonary resuscitation within 2 weeks; noncompressible arterial or central venous punctures within 24 h; and significant anemia or thrombocytopenia. Informed consent was obtained from each patient in accordance with the requirements of each hospital's Institutional Review Board.

Study design and protocol. The trial was designed as a phase II, randomized, dose escalation trial between hirudin and heparin. The plan for the randomization and dose escalation was as follows: For the first dose of hirudin, 100 patients were enrolled, 50 to receive hirudin and 50 to receive heparin. Safety and efficacy data for the hirudin dose group were compared with the heparin dose group at the end of the first dose. If no safety concerns were identified, the next dose of hirudin was tested. In each subsequent hirudin dose group, 30 patients were enrolled. To gain more experience with the final hirudin dose, 50 patients were enrolled in a fourth dose group. To have concurrent control subjects but to maximize the numbers of patients treated with hirudin, 10 heparin-treated patients were enrolled in each subsequent hirudin dose group, making the randomization ratios between hirudin and heparin of 1:1, 3:1, 3:1 and 5:1 for the four hirudin doses, respectively. All patients were randomized by a central telephone system.

The protocol is outlined in Figure 1. Open-label study drug was administered as a bolus before the start of thrombolytic therapy, followed immediately by an infusion for 5

days. The four ascending dose groups of hirudin (recombinant desulfatohirudin [CGP 39393] Ciba-Geigy) were as follows: 0.15-mg/kg body weight intravenous bolus, followed by a 0.05-mg/kg per h fixed infusion; 0.1-mg/kg bolus followed by a 0.1-mg/kg per h fixed infusion; 0.3-mg/kg bolus followed by a 0.1-mg/kg per h fixed infusion; and 0.6-mg/kg bolus followed by a 0.2-mg/kg per h fixed infusion. The hirudin infusion was not adjusted on the basis of activated partial thromboplastin time; however, as a safety measure, if an activated partial thromboplastin time after 24 h was >150 s, the infusion rate was halved. Heparin (Liquaemin, Organon Inc.) was administered as a 5,000-IU intravenous bolus followed by a 1,000-IU/h infusion that was then adjusted to maintain an activated partial thromboplastin time between 65 and 90 s on the Ciba-Corning Biotrack 512 coagulation monitor (Ciba-Corning Diagnostics Corporation) according to a standardized nomogram adapted from Hirsh (16). Blood samples were obtained for activated partial thromboplastin time measurements at baseline and 6, 12 and 24 h after the start of thrombolytic therapy and every 12 h thereafter while patients remained on study drug. Repeat measurements of activated partial thromboplastin time were obtained 4 to 6 h after adjustments in the heparin infusion. The hirudin or heparin infusion was continued for 5 days unless the patient experienced major hemorrhage, reinfarction or severe recurrent ischemia requiring angioplasty or coronary bypass surgery.

All patients received front-loaded t-PA (Activase, Genentech) with a 15-mg bolus, 0.75-mg/kg (up to 50 mg) infusion over 30 min, followed by a 0.50-mg/kg (up to 35 mg) infusion over 60 min (17) and aspirin (160 mg) chewed immediately on enrollment, if patients were not already taking aspirin, and 160 mg daily thereafter. Patients also received intravenous, followed by oral metoprolol tartrate (Lopressor, Ciba-Geigy) if there were no contraindications (bradycardia, hypotension, atrioventricular block or bronchospastic lung disease) (18). Nitrates, calcium antagonists and other medications were administered at the discretion of the treating physician.

Patients underwent coronary arteriography to ascertain infarct-related artery patency at 90 min after the start of thrombolytic therapy. The arterial sheath for the catheterization was secured in place, and repeat coronary arteriography was performed 18 to 36 h after the start of thrombolytic therapy (or earlier if the patient experienced recurrent ischemic pain with ST segment elevation). If the infarct-related artery was occluded at 90 min (TIMI grade 0 or 1 flow) (1), and after coronary occlusion was confirmed at 120 min, rescue coronary angioplasty could be performed at the discretion of the treating physician. If angioplasty was performed, the study drug (hirudin or study-supplied heparin) was discontinued, and further anticoagulation with heparin was determined by the treating physician. Coronary arteriography at 18 to 36 h was not required if the patient underwent rescue angioplasty. Revascularization with angioplasty or coronary artery bypass surgery was recommended only if significant recurrent ischemia developed and was performed at the discretion of the treating physician (18). Coronary perfusion was evaluated according to the TIMI perfusion grading system (1) by investigators at the angiographic core laboratory who were unaware of treatment assignment.

During the hospital period, patients were monitored for recurrent ischemic pain lasting ≥30 min, for which serial ECGs and creatine kinase (CK) isoenzymes were obtained during the subsequent 24 h to document reinfarction. The ECGs and enzyme measurements were submitted with a narrative summary to investigators at the myocardial infarction confirmation core laboratory who were unaware of treatment assignment.

Study end points. The primary efficacy end point was the achievement of TIMI grade 3 flow at both 90 min and 18 to 36 h without death or reinfarction before the 18- to 36-h angiogram. Patients were prespecified as "efficacy evaluable" if they underwent both angiograms during study drug therapy or met a primary efficacy end point before the 18- to 36-h angiogram. Prespecified secondary end points were the incidence of death or reinfarction, TIMI grade 3 flow, TIMI grade 2 or 3 flow at 90 min and 18 to 36 h and angiographic reocclusion.

The primary safety end point was the occurrence of major hemorrhage, defined as either an intracranial hemorrhage or bleeding associated with a decrease in hemoglobin ≥5 g/dl or absolute decrease in hematocrit ≥15% (e.g., hematocrit decrease from 40% to 25%) (19) or anaphylaxis. Secondary safety end points were the occurrence of hemorrhagic pericardial tamponade or nonhemorrhagic stroke (19,20). All patients who received the study drug were included in the safety analyses.

End point definitions. Recurrent infarction occurring within the 1st 18 h after the start of thrombolytic therapy was prospectively defined as recurrent ischemic pain at rest lasting at least 30 min associated with new or recurrent ST segment elevation ≥0.1 mV in at least two contiguous ECG leads (19). Criteria for cardiac enzymes were not included in the definition of recurrent myocardial infarction during the 1st 18 h because cardiac enzymes were still increasing from the index myocardial infarction. After 18 h, recurrent infarction was defined as recurrent ischemic pain lasting at least 30 min associated with either ECG or enzyme evidence of reinfarction. The ECG evidence of reinfarction was defined as either major (≥0.03 ms) new Q waves in two or more leads or new left bundle branch block in the absence of any previous left bundle branch conduction defect. Enzyme evidence of reinfarction was defined as 1) total CK greater than twice the upper limit of normal and increased by at least 25% over the previous value (qualitative creatine kinase, MB fraction [CK-MB] was required to be positive [i.e., above the upper limit of normal] when available, and CK-MB took precedence over total CK); or 2) total CK less than twice the upper limit of normal but exceeding the upper limit of normal by at least 50% and increased by at least 50% over the

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Table 1. Baseline Characteristics of Study Patients

	Hirudin						
	0.15 B/0.05 Inf (n = 50)	0.1 B/0.1 Inf (n = 33)	0.3 B/0.1 Inf (n = 29)	0.6 B/0.2 Inf (n = 50)	All Doses (n = 162)	Heparin (n = 84)	p Value*
Age (yr)	55.3 ± 10.1	57.4 ± 11.0	57.8 ± 10.4	55.5 ± 9.0	56.2 ± 10.0	57.6 ± 9.9	0.30
Age ≥70 yr (%)	6.0	12.1	20.7	6.0	9.9	7.1	0.48
Gender (% male)	62.0	75.8	65.5	70.0	74.1	78.6	0.35
Race (% white)	88.0	87.9	86.2	72.0	82.7	84.5	0.72
Not low risk (%)†	56.0	57.6	55.2	58.0	56.8	42.9	0.04
Previous MI (%)	12.0	30.3	10.3	14.0	16.0	13.1	0.54
Anterior MI (%)	46.0	33.3	34.5	46.0	40.7	27.4	0.03
Previous angina (%)	32.0	42.4	27.6	30.0	32.7	31.0	0.78
Previous CHF (%)	0	0	3.4	0	0.6	0	0.47
Hypertension (%)	24.0	45.5	51.7	28.0	35.2	27.4	0.25
Diabetes (%)	8.0	9.1	17.2	12.0	11.1	14.3	0.47
Smoking (%)	78.0	81.8	75.9	82.0	80.2	72.6	0.21
Time from onset of pain to arrival at hospital (h:min)	1:44 ± 1:05	2:15 ± 1:23	2:01 ± 1:17	1:41 ± 0:55	1:52 ± 1:07	1:30 ± 0:56	0.01
Time from arrival at hospital to treatment (h:min)	1:36 ± 0:52	1:21 ± 0:46	1:29 ± 0:42	1:22 ± 0:41	1:27 ± 0:45	1:08 ± 0:28	< 0.001
Overall time to treatment (h:min)	3:20 ± 1:21	3:35 ± 1:29	3:30 ± 1:32	3:03 ± 1:10	3:19 ± 1:22	2:38 ± 1:05	< 0.001

*Heparin versus all hirudin. †TIMI Study Group (18). Values presented are mean value ± SD or percent of patients. B = bolus (mg/kg); CHF = congestive heart failure; Inf = intravenous infusion (mg/kg per h); MI = myocardial infarction.

previous value (qualitative CK-MB was required to be positive when available, and CK-MB took precedence over total CK) (19).

Sample size considerations and statistical analyses. This pilot trial was designed to provide an initial experience with hirudin and thrombolytic therapy, and the sample size was not based on statistical considerations to determine a definitive difference in efficacy or safety between the two treatments. Descriptive statistics with regard to the prespecified study end points were to be computed. As each of the four doses were compared with heparin, it was noted that for the end points evaluated, each dose group had similar effects. With the similar effects in each dose group, an analysis pooling the four hirudin dose groups was carried out. Statistical comparisons across the four hirudin dose groups failed to detect any major differences in baseline characteristics or angiographic or clinical outcomes, lending support to the pooling of the doses. Thus, mainly for descriptive purposes, p values are included between all hirudin-treated patients compared with heparin-treated patients. In addition, no significant variations were noted by clinical centers in the primary efficacy or safety end points.

Statistical comparisons were made by chi-square analysis for categoric variables and with Student *t* tests for continuous variables, which are presented as mean value ± SD. Differences in activated partial thromboplastin times were compared using the Kruskal-Wallis test (21).

Results

Patients. A total of 252 patients were identified as eligible and were enrolled in the trial. Six patients (two heparin-treated patients [2.3%], four hirudin-treated patients [2.4%]) did not undergo the initial coronary angiogram. The reasons for exclusion were lack of an available cardiac catheterization laboratory (four patients) and lack of a diagnosis of acute myocardial infarction on review by the TIMI investigator (two patients). These six patients were thus not included in the efficacy analyses, leaving 246 patients. However, because they had received the study drug, all 252 patients were included in the safety analyses.

Baseline characteristics. Despite randomization, the hirudin-treated patients had a somewhat poorer clinical profile than the heparin-treated patients (Table 1). The percent of patients that were "not low risk," as defined in TIMI II (18) (age ≥70 years, previous myocardial infarction, anterior myocardial infarction, hypotension with sinus tachycardia, atrial fibrillation or left bundle branch block) was higher for hirudin (56.8%) compared with heparin (42.9%) ($p = 0.04$). Anterior infarction was present in 40.7% of hirudin-treated patients compared with 27.4% of heparin-treated patients ($p = 0.03$). The average time from symptom onset to treatment with thrombolytic therapy was 41 min longer for the hirudin group ($p < 0.001$). This delay comprised a 22-min longer time between onset of symptoms and arrival at hospital and a 19-min delay between arrival and start of thrombolytic therapy. However, despite the sequential nature of this dose escalation trial, there were no significant differences between the four hirudin dose groups with respect to the major baseline characteristics or time to treatment.

Coronary angiography. The primary end point of the trial was the presence of TIMI grade 3 flow (1) at both 90 min and 18 to 36 h after the start of thrombolytic therapy, without

Table 2. Angiographic Results

	Hirudin											
	0.15 B/0.05 Inf		0.1 B/0.1 Inf		0.3 B/0.1 Inf		0.6 B/0.2 Inf		All Doses		Heparin		p Value*
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
90 min and 18–36 h													
Efficacy-evaluable pts†	49		30		29		49		157		79		
Primary end point: TIMI grade 3 flow at both time points (without death or MI before 18–36-h angiogram)	32	65.3	20	66.6	15	51.7	30	61.2	97	61.8	39	49.4	0.07
90 min													
Pts with angiograms	50		33		29		50		162		84		
TIMI 3 flow	33	66.6	24	72.7	16	55.2	32	64.0	105	64.8	48	57.1	0.24
TIMI 2 or 3 flow	42	84.0	27	81.8	23	79.9	42	84.0	133	82.1	66	78.6	0.50
18–36 h													
Pts with angiograms‡	39		26		23		44		132		65		
TIMI 3 flow	34	87.2	20	76.9	21	95.5	36	80.0	111	84.1	48	73.8	0.09
TIMI 2 or 3 flow	39	100.0	24	92.3	22	100.0	44	97.8	129	97.8	58	89.2	0.01

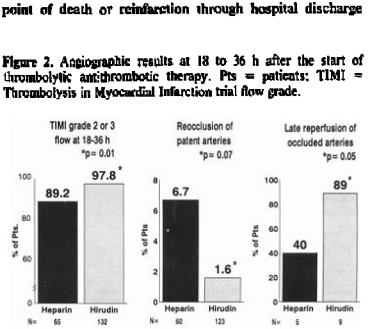
*Heparin versus all hirudin. †Patients were prespecified as efficacy evaluable if they underwent both angiograms while receiving the study drug or met a primary efficacy end point before the 18- to 36-h angiogram. Five heparin-treated and five hirudin-treated patients were not evaluable because no 18- to 36-h angiogram was available. Reasons were hemorrhage at the instrumented site (two hirudin-treated and three heparin-treated patients); angioplasty for persistent ischemia (one heparin-treated patient); and miscellaneous reasons (three hirudin-treated and one heparin-treated patient). ‡Patients did not undergo angiography at 18 to 36 h for the following reasons: 1) not required by protocol after rescue angioplasty (15 hirudin-treated and 10 heparin-treated patients); 2) hemorrhage at the instrumented site (three hirudin-treated and three heparin-treated patients); 3) angioplasty for persistent ischemia at 90 min (one heparin-treated patient); 4) emergent bypass surgery due to left main coronary artery stenosis (two hirudin-treated patients); 5) medical instability due to cardiogenic shock (one heparin-treated patient) or recurrent myocardial infarction (one hirudin-treated patient); 6) death (one hirudin-treated patient); or 7) miscellaneous reasons (eight hirudin-treated and four heparin-treated patients). All but 10 (4.1%) of these patients had met a component of the primary efficacy end point and thus were evaluable. Values presented are number of patients (%). IV = intravenous; pts (Pts) = patients; TIMI = Thrombolysis in Myocardial Infarction trial flow grade; other abbreviations as in Table 1.

death or reinfarction before the 18- to 36-h angiogram. This was achieved in 97 (61.8%) of 157 evaluable hirudin-treated patients compared with 39 (49.4%) of 79 evaluable heparin-treated patients ($p = 0.07$) (Table 2). Angiography at 90 min demonstrated that TIMI grade 3 flow was achieved in 105 (64.8%) of 162 hirudin-treated patients compared with 48 (57.1%) of 84 heparin-treated patients (p = NS) (Table 2). TIMI grade 2 or 3 flow was achieved in 133 (82.1%) of 162 hirudin group patients compared with 66 (78.6%) of 84 heparin group patients (p = NS). There were no significant differences in TIMI flow grade between the four dose groups of hirudin.

After 18 to 36 h of antithrombotic therapy, differences between heparin and hirudin were more apparent: In patients undergoing follow-up angiography, TIMI grade 3 flow was present in 111 (84.1%) of 132 hirudin-treated patients and in 48 (73.8%) of 65 heparin-treated patients ($p = 0.09$), and TIMI grade 2 or 3 flow was present in 129 (97.8%) of 132 hirudin-treated patients compared with 58 (89.2%) of 65 heparin-treated patients ($p = 0.01$) (Table 2). The improved infarct-related artery patency observed at 18 to 36 h in hirudin-treated patients was based on two mechanisms: decreased reocclusion of patent arteries and improved late reperfusion of occluded arteries. In patients who had a patent infarct-related artery at 90 min, reocclusion occurred in 2 (1.6%) of 123 hirudin-treated patients compared with 4 (6.7%) of 60 heparin-treated patients ($p = 0.07$) (Fig. 2). Fourteen patients who had an occluded infarct-related artery at 90 min after thrombolysis did not undergo rescue angioplasty for reasons determined by the treating physicians. Of these, eight of nine hirudin-treated patients achieved TIMI grade 2 or 3 flow at 18 to 36 h compared with two of five heparin-treated patients ($p = 0.05$) (Fig. 2).

Effect on mortality and reinfarction. The clinical end point of death or reinfarction through hospital discharge

Figure 2. Angiographic results at 18 to 36 h after the start of thrombolytic antithrombotic therapy. Pts = patients; TIMI = Thrombolysis in Myocardial Infarction trial flow grade.



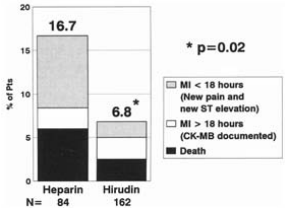


Figure 3. Death or reinfarction through hospital discharge. CK-MB = creatine kinase, MB fraction; other abbreviations as in Figures 1 and 2.

occurred in 14 (16.7%) of 84 of heparin-treated patients compared with 11 (6.8%) of 162 hirudin-treated patients ($p = 0.02$) (Fig. 3). In-hospital mortality was low in hirudin-treated patients (2.5%), whereas mortality was 6.0% in heparin-treated patients (Table 3). Reinfarction (fatal and nonfatal) was also lower in hirudin-treated patients (4.3% vs. 11.9%, $p = 0.03$). During the 48 h after study drug discontinuation, one hirudin-treated patient (0.6%) and one heparin-treated patient (1.2%) experienced reinfarction, indicating that there was no evidence of so-called rebound (22,23). Recurrent ischemic pain lasting at least 30 min, without enzymatic or ECG evidence of reinfarction, occurred in 5 (6.0%) of 84 heparin-treated patients compared with 7 (4.3%) of 162 hirudin-treated patients (p = NS), all of whom were in the first hirudin dose group.

Revascularization procedures. The number of patients who underwent revascularization with angioplasty or bypass surgery during the hospital period was significantly lower for hirudin-treated patients (32.1%) compared with heparin-treated patients (50.0%) ($p = 0.006$) (Table 3). This difference was largely due to a difference in the rate of angioplasty (26.5% for hirudin vs. 42.9% for heparin, $p = 0.009$). Rescue angioplasty of a persistently occluded coronary artery was performed in a similar proportion of patients: 15 (51.7%) of 29 hirudin-treated patients and 10 (55.5%) of 18 heparin-treated patients (p = NS), which represented 9.3% and 11.9% of the total number of hirudin-treated and heparin-treated patients, respectively. Fewer hirudin-treated patients, however, underwent angioplasty for reocclusion or recurrent ischemia with ST segment elevation within the 1st 24 h (3.1% vs. 9.6%, $p = 0.03$). The remainder of the difference in revascularization involved angioplasty after 24 h. Although this trial was not designed to evaluate the effects of hirudin on angioplasty, it is of interest that 4 of 36 heparin-treated patients, compared with none of 43 hirudin-treated patients experienced reinfarction in the 24 h after angioplasty ($p = 0.02$). These reinfarctions occurred after rescue angioplasty in two patients, angioplasty for recurrent ischemia in one patient and one elective procedure.

Safety end points. Major spontaneous hemorrhage during the hospital course occurred in 4.7% of heparin-treated patients and 1.2% of hirudin-treated patients ($p = 0.09$) (Table 4). There was one intracranial hemorrhage in the heparin group and none in the hirudin group. The total incidence of major hemorrhage was 23.3% for heparin compared with 17.5% for hirudin overall (p = NS). Major hemorrhage at an instrumented site occurred in 18.6% of patients who received heparin and 16.3% of those who received hirudin (p = NS). Hemorrhage at an instrumented site occurred in 29.4% of patients receiving the highest dose of hirudin (p = NS compared with heparin). No patients developed a thrombotic or embolic stroke. Anaphylaxis was not observed during the 5-day infusion period in either heparin- or hirudin-treated patients.

Table 3. In-Hospital Incidence of Death, Reinfarction and Revascularization Procedures

	Hirudin											
	0.15 BU/0.05 Inf (n = 50)		0.1 BU/0.1 Inf (n = 33)		0.3 BU/0.1 Inf (n = 29)		0.6 BU/0.2 Inf (n = 50)		All Doses (n = 162)		Heparin (n = 84)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Death	1	2.0	0	0	2	6.9	1	2.0	4	2.5	5	6.0
Reinfarction												
Total	3	6.0	1	3.0	1	3.4	2	4.0	7	4.3	10	11.9
<18 h	1	2.0	0	0	1	3.4	1	2.0	3	1.9	7	8.3
>18 h	2	4.0	1	3.0	0	0	1	2.0	4	2.5	3	3.6
Death or reinfarction	4	8.0	1	3.0	3	10.3	3	6.0	11	6.8	14	16.7
Total PTCA	12	24.0	9	27.3	7	24.1	15	30.0	43	26.5	36	42.9
Rescue PTCA	5	10.0	3	9.1	4	13.8	3	6.0	15	9.3	10	11.9
PTCA for reocclusion/ischemia <24 h	2	4.0	1	3.0	1	3.4	1	2.0	5	3.1	8	9.6
PTCA >24 h	5	10.0	5	15.2	2	6.9	11	22.0	23	14.2	18	21.4
CABG	4	8.0	1	3.0	1	3.4	6	12.0	12	7.4	8	9.5
PTCA or CABG	16	32.0	10	30.3	8	27.6	18	36.0	52	32.1	42	50.0

p Value*
0.17
0.03
0.01
0.62
0.02
0.009
0.51
0.03
0.15
0.56
0.006

*Heparin versus all hirudin. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

Table 4. Primary Safety End Point

	Hirudin											
	0.15 B/0.05 Inf		0.1 B/0.1 Inf		0.3 B/0.1 Inf		0.6 B/0.2 Inf		All Doses		Heparin	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	p Value*
Safety-evaluable pts	52		34		29		51		166		86		
Major spontaneous hemorrhage	1	1.9	1	2.9	0	0	0	0	2	1.2	4	4.7	0.09
Major hemorrhage at an instrumented site	6	11.5	2	5.9	4	13.8	15	29.4	27	16.3	16	18.6	0.64
Total major hemorrhage	7	13.5	3	8.8	4	13.8	15	29.4	29	17.5	20	23.3	0.27

*Heparin versus all hirudin. Abbreviations as in Table 1.

Hematologic findings. The median activated partial thromboplastin time values over time are shown in Table 5. At 24 h, the median activated partial thromboplastin time in the 0.05-mg/kg per h hirudin dose group was similar to that of heparin (63 s), whereas that for the 0.2-mg/kg per h hirudin dose was 85 s ($p < 0.001$ across the four hirudin doses). During the 1st 12 h, 31.8% of heparin-treated patients had an activated partial thromboplastin time <60 s compared with 7.8% of hirudin-treated patients ($p < 0.001$). During the study drug infusion period, after removal of the sheaths for the second catheterization, the percent of patients who had an activated partial thromboplastin time that varied by <30 s (similar to the target range of activated partial thromboplastin time) during the study drug infusion period was 36.2% for hirudin-treated patients compared with 12.8% for heparin-treated patients ($p = 0.004$) (Table 5). Using a range of 40 s, 55.0% of hirudin-treated patients maintained a stable activated partial thromboplastin time compared with 19.1% of heparin-treated patients ($p = 0.002$).

Discussion

Although thrombolytic therapy achieves early coronary reperfusion, numerous procoagulant factors, the most important being thrombin (24,25), are activated and can lead to reocclusion or reinfarction. Because hirudin can inhibit clot-bound thrombin (26) and is better able to inhibit thrombin-mediated platelet activation than heparin (8,15), its more potent antithrombotic effects could be expected to improve coronary patency and clinical outcome. The TIMI 5 trial examined the effects of the specific thrombin inhibitor hirudin in patients with acute myocardial infarction treated with t-PA and aspirin. In this pilot trial, hirudin, compared with heparin, appeared to provide more stable anticoagulation, decreased reocclusion and greater infarct-related artery patency at the later time point and, most important, fewer clinical events (death or reinfarction). With the insights gained into the effects of hirudin on coronary reperfusion and clinical outcome, this trial provides a strong rationale for proceeding to larger trials to definitively evaluate the clinical impact of hirudin after thrombolytic therapy.

TIMI grade 3 flow. The achievement of TIMI grade 3 flow at either 90 min or 18 to 36 h has been shown by several investigative groups to be associated with improved myocardial salvage (27,28), a lower rate of reocclusion (29,30), improved left ventricular function (27,31) and, most important, improved survival (3,4,32,33). At the 90-min angiogram, there was a nonsignificant trend for TIMI grade 3 flow favoring hirudin over heparin (64.8% vs. 57.1%). Hirudin demonstrated a greater advantage in what might be termed optimal thrombolysis, that is, the achievement of TIMI grade 3 flow at both 90 min and 18 to 36 h (without death or reinfarction), with 61.8% of hirudin-treated patients having this successful outcome compared with 49.4% of heparin-

Table 5. Results of Activated Partial Thromboplastin Time Tests

	Median APTT (s) (25th, 75th percentiles)					
	Hirudin					
Time Point	0.15 B/0.05 Inf	0.1 B/0.1 Inf	0.3 B/0.1 Inf	0.6 B/0.2 Inf	All Doses	Heparin
Baseline	34 (31, 38)	35 (3, 31)	26 (23, 28)	25 (18, 31)	—	23 (19, 28)
6 h	74 (54, 90)	95 (76, 115)	77 (67, 122)	102 (93, 122)	—	100 (59, 149)
12 h	73 (65, 88)	83 (73, 110)	88 (72, 110)	107 (92, 119)	—	76 (59, 123)
24 h	63 (55, 75)	79 (66, 102)	76 (58, 85)	85 (75, 109)	—	63 (48, 75)
48 h	60 (57, 89)	76 (67, 83)	77 (61, 94)	91 (76, 104)	—	63 (51, 86)
72 h	64 (51, 77)	74 (61, 100)	75 (61, 94)	89 (75, 103)	—	60 (53, 72)
96 h	60 (52, 70)	63 (62, 71)	71 (62, 85)	87 (75, 97)	—	68 (58, 87)
120 h	60 (51, 73)	63 (41, 68)	57 (57, 57)	87 (83, 97)	—	73 (60, 80)
Pts with range of APTT ≤30 s	48.5%	26.3%	27.7%	30.0%	36.2%	12.8%
Pts with range of APTT ≤40 s	69.7%	47.4%	44.4%	40.0%	55.0%	19.1%

APTT = activated partial thromboplastin time; other abbreviations as in Tables 1 and 2.

treated patients ($p = 0.07$). This improvement in early and sustained TIMI grade 3 flow may explain, at least in part, the favorable clinical outcome observed for hirudin-treated patients in this trial.

Coronary patency at 90 min. Although a trend in favor of hirudin for TIMI grade 3 flow was observed at 90 min, patency of the infarct-related artery (TIMI grade 2 or 3 flow) was similar between hirudin and heparin. The absence of a greater advantage in early patency for hirudin may have been influenced by several factors: 1) The 90-min angiographic time point may be too short a period for an antithrombin to exhibit effectiveness; 2) the primary therapy of t-PA may predominate over the effect of anticoagulant therapy at this early time point, as was noted by Topol *et al.* (34) in a randomized trial that demonstrated no difference in initial patency with or without immediate intravenous heparin; and 3) a bolus dose of either heparin or hirudin prolongs activated partial thromboplastin time >110 s for the 1st 90 min (12,35), which may provide a sufficient degree of anticoagulation for achievement of maximal 90-min patency.

Coronary patency at 18 to 36 h. A major finding of this study is that hirudin significantly improved infarct-related artery patency at 18 to 36 h compared with heparin. Only 2.2% of hirudin-treated patients had an occluded artery at 18 to 36 h compared with 10.8% of heparin-treated patients ($p = 0.01$). There is substantial evidence that successful achievement of an open artery is beneficial to the long-term outcome of patients after thrombolytic therapy (36–39). The beneficial effect of hirudin on infarct-related artery patency may prove to be an important mechanism of benefit over current thrombolytic-antithrombotic regimens.

Improved patency with hirudin was achieved by two mechanisms: decreased reocclusion and improved late reperfusion. Hirudin demonstrated a strong trend toward preventing reocclusion before the 18- to 36-h catheterization (1.6% for hirudin vs. 6.7% for heparin). Because reocclusion has been associated with a nearly threefold increase in mortality (5), the advantage of hirudin over heparin in preventing reocclusion may be one of the mechanisms for its clinical benefit.

An intriguing difference in the efficacy of hirudin and heparin was noted in the small number of patients with an occluded coronary artery at 90 min who did not undergo rescue angioplasty. Eight of nine hirudin-treated patients achieved reperfusion by 18 to 36 h compared with two of five heparin-treated patients. In patients with failed initial reperfusion, two approaches have been pursued. Rescue angioplasty has shown modest clinical benefit (40,41), but it requires rapid availability of skilled angiographers and may lead to increased bleeding compared with a more conservative approach (42,43), and "rescue thrombolysis" with a second dose of a thrombolytic agent (44) may incur the increased bleeding seen with high doses of thrombolytic agents in previous trials (18). If hirudin is found in a larger number of patients to increase late reperfusion of initially occluded coronary arteries, aggressive adjunctive therapies, such as rescue angioplasty or additional thrombolysis, may not be necessary.

Effect on death and reinfarction. Although this trial was not designed to detect differences in mortality or reinfarction, a marked reduction in the rate of death or reinfarction was observed (16.7% for heparin vs. 6.8% for hirudin, $p = 0.02$). The beneficial effects observed in achieving and maintaining patency of the infarct-related artery appear to translate into important clinical benefits for both death and reinfarction. In addition, there was no increase in recurrent ischemic events (i.e., so-called rebound) in the early days after discontinuation of hirudin, as has been noted after heparin or argatroban therapy for unstable angina (22,23). This may be because of the binding characteristics of hirudin (45), or because all patients received aspirin (23). The effect of hirudin was most dramatic in reducing reinfarction within the 1st 18 h after thrombolysis, the time period when reocclusion commonly is observed (5). More than 8% of heparin-treated patients experienced prolonged, recurrent ischemic pain and new ST segment elevation compared with 1.9% of hirudin-treated patients ($p = 0.01$). This finding is consistent with animal data showing more stable reperfusion with hirudin and less transient opening and closing of the infarct-related artery during the initial hours (11,46). Early stabilization of the coronary lesion may also explain the improved patency that was observed at 18 to 36 h.

It should be pointed out, however, that the rate of reinfarction was higher in the heparin arm of this trial than that reported in other clinical trials. This probably relates to the prespecified definition of myocardial infarction within the 1st 18 h, which required new ischemic pain lasting >30 min and new ST segment elevation. However, if the definition of myocardial infarction from the Primary Angioplasty in Myocardial Infarction trial (47) is used, which requires either enzymatic evidence of reinfarction or angiographic reocclusion, a similar reduction in death or myocardial infarction is observed (13.1% for heparin vs. 4.9% for hirudin, $p = 0.02$).

Effective anticoagulation. An additional potential advantage of hirudin is its ability to establish more consistent anticoagulation, which is critically important for maintaining patency after thrombolysis (35,48,49). Because hirudin is not inhibited by activated platelets or other proteins that are known to neutralize heparin (16,50), it may result in a greater consistency of anticoagulation (16,50). In this trial, hirudin achieved effective anticoagulation during the 1st 12 h, defined as all activated partial thromboplastin time values >60 s, in 92.2% of patients compared with only 68.2% of heparin-treated patients ($p < 0.001$). In addition, despite a maximized heparin regimen with very frequent monitoring and use of a standardized heparin nomogram (16), >80% of heparin-treated patients had fluctuations in the activated partial thromboplastin time exceeding a range of 40 s. The relative consistency of anticoagulation achieved with hirudin may represent an important mechanism for its improved efficacy. Furthermore, the fixed dosing without need for

frequent monitoring will allow use of effective intravenous anticoagulation in hospitals where the resources for close titration of intravenous heparin are not available.

Relation of hirudin dose to outcome. Although this trial was a dose-ranging trial of hirudin, the absolute number of patients in each dose group was small, thus limiting the statistical power to compare individual doses. Although each of the four doses of hirudin resulted in relatively similar angiographic and clinical outcomes (Tables 2 and 3), because of the limited sample size, a dose response in efficacy can neither be confirmed nor excluded from these data. The four doses did lead to a dose-dependent increase in the activated partial thromboplastin time, as well as a nonsignificant increase in instrumented site hemorrhage at the highest dose, the latter finding demonstrating that this was most likely the maximal safe dose of hirudin. Conversely, spontaneous hemorrhage was rare (1%) in hirudin-treated patients, indicating that in noninstrumented patients even the highest dose could be expected to be well tolerated.

Limitations of the study. There are several potential limitations of this study that should be considered. First, this was an open-label pilot trial designed primarily to assess the safety of hirudin when given in conjunction with thrombolytic therapy. We did find that hirudin was well tolerated and were encouraged to find favorable trends for hirudin in efficacy end points. However, these need to be confirmed in larger numbers of patients. Second, the trial was a dose escalation study using four different doses of hirudin. Because findings were similar between the hirudin doses, for the purposes of comparison with heparin, all doses of hirudin were combined. For a definitive comparison with heparin, a single dosing regimen of hirudin should be used. Third, a major end point of the trial was to assess coronary patency angiographically. It is possible that the end points of death, reinfarction and major hemorrhage could have been influenced by the protocol design. Fourth, the imbalance in the baseline characteristics may have influenced the results, but this would have favored heparin, not hirudin. Finally, although the important clinical end point of death or reinfarction was significantly reduced in hirudin-treated patients, the absolute number of events was small, reemphasizing the need to test hirudin in a larger patient cohort.

Conclusions. In this pilot trial of patients with acute myocardial infarction treated with front-loaded t-PA and aspirin, hirudin appears to offer several advantages over heparin. Hirudin improved the combination of early and sustained TIMI grade 3 flow as well as coronary patency at 18 to 36 h and led to a more stable clinical course, with reduced in-hospital death or reinfarction. Hirudin provided a more stable activated partial thromboplastin time without adjustment of dose and was not associated with an increase in major hemorrhage. Hirudin is thus a promising adjunctive agent to thrombolytic therapy, and a larger trial is warranted to provide a definitive comparison between hirudin and heparin.

Appendix

Thrombolysis in Myocardial Infarction (TIMI) 5 Trial Investigators and Clinical Centers

Study Chairman's Office: Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. *Study Chairman*, Eugene Braunwald, MD; *Coinvestigator*, Christopher P. Cannon, MD; *Project Director*, Carolyn H. McCabe, BS; *Study Coordinator*, Tia DeFeo-Fraulini, MS.

Angiographic Core Laboratory: Brown University, Providence, Rhode Island. *Principal Investigators*, David O. Williams, MD, Barry L. Sharaf, MD; *Coinvestigator*, Brynmor S. Riley, MD; *Research Coordinators*, Paula Ferreira, RN, Nicholas Miele, BA.

Biochemical Core Laboratories, MB isoforms: Baylor College of Medicine, Houston, Texas: *Principal Investigator*, Peter Pulse, MD; *Coinvestigator*, Robert Roberts, MD; **MM isoforms:** Washington University, St. Louis, Missouri. *Principal Investigator*, Dana Abendschein, PhD; *Laboratory Director*, Lea Bullock.

Coagulation Core Laboratory: Brigham and Women's Hospital, Boston, Massachusetts. *Principal Investigator*, Joseph Loscalzo, MD, PhD; *Research Coordinator*, Florinda George.

Myocardial Infarction Confirmation Core Laboratory: St. Louis University, St. Louis, Missouri. *Principal Investigator*, Bernard Chaitman, MD; *Coinvestigator*, Beaver Tamesis, MD; *Research Coordinators*, Leslee Shaw, MS, Karen Stocke, BS, MBA, Deborah Kargl, BS.

Radionuclide Core Laboratory: Yale University School of Medicine, New Haven, Connecticut. *Principal Investigators*, Barry Zaret, MD, Frans Wackers, MD; *Research Coordinators*, Michael McMahon, Patty Atkinson, Jennifer Mutter, RTNM.

Steering Committee: The members of the Steering Committee are the Study Chairman and the Principal Investigators from the TIMI 5 clinical centers and core laboratories.

Sponsor: Ciba-Geigy Corporation, Summit, New Jersey. *Project Director*, Marc Henis, MD; *Clinical Monitor*, Susan Edwards, MS; *Statisticians*, John Castellano, PhD, Paul Gallo, PhD.

Data and Safety Monitoring Board: Lewis Becker, MD, Joel Karliner, MD, Sheryl Kelsey, PhD, Charles Rackley, MD, Sanford Shattil, MD; *Ex-Officio Members*, Eugene Braunwald, MD, Malcolm McNab, MD.

*Clinical Centers**

Brown University, Providence, Rhode Island. *Principal Investigator*, David O. Williams, MD; *Coinvestigators*, Barry L. Sharaf, MD, George R. McKendall, MD, Edward Thomas, MD, Thomas Drew, MD; *Research Coordinators*, Louise Erikson, RN, Paula Ferreira, RN.

University of Minnesota–Hennepin County Medical Center, Minneapolis, Minnesota. *Principal Investigator*, Timothy D. Henry, MD; *Research Coordinator*, Charlene Berger, RN; **The Methodist Hospital, St. Louis Park, Minnesota.** *Principal Investigator*, J. Mark Haugland, MD; *Research Coordinator*, Tracy Oatcle, RN.

University of Alabama at Birmingham, Birmingham, Alabama. *Principal Investigator*, William J. Rogers, MD; *Coinvestigators*, Douglas J. Pearce, MD, Gilbert Perry, MD, Silvio Papapietro, MD; *Research Coordinators*, Terry Morgan, RN, Cynthia Craven, RN.

Baystate Medical Center, Springfield, Massachusetts. *Principal Investigator*, Marc J. Schweiger, MD; *Coinvestigators*, Mark Porway, MD, John Jocelson, MD, Thomas Marantz, MD, J. Mark Peterman, MD; *Research Coordinator*, Deborah Warwick, RN.

University of Virginia Health Sciences Center, Charlottesville, Virginia. *Principal Investigator*, Robert S. Gibson, MD; *Coinvestigator*, Eric Powers, MD; *Research Coordinators*, Sharon Sayre, BSN, Nancy Fauber, MSN, Margaret Ball, BSN.

Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York. *Principal Investigator*, Hiltrud S. Mueller, MD; *Coinvestigators*, Mark A. Greenberg, MD, Mark A. Menegus, MD, Mark H. Goldberger, MD; *Research Coordinators*, Kathleen Hemingway, RN, Barbara Ventura, RN, Joseph Cosico, RN; **Winthrop-University Hospital, Mineola, New York.** *Principal investigator*, Richard M. Steingart, MD; *Coinvestigators* Anthony Gambino, MD, Steven Zeldis, MD, Robbin Moino, MD, Philip Ragno, MD; *Research Coordinators*, Suzanne Bilodeau, RN, Mary Ellen Coglianese, RN.

*Clinical centers are listed in order of number of patients enrolled.

University of Utah, LDS Hospital, Salt Lake City, Utah. *Principal Investigator*, Jeffrey L. Anderson, MD; *Coinvestigators*, Labros Karagounis, MD, Fidala Moreno, MD, Miguel Gomez, MD; *Research Coordinator*, Ann Allen, RN.

University of Massachusetts Medical Center, Worcester, Massachusetts. *Principal Investigator*, Richard C. Becker, MD; *Research Coordinators*, Steve Ball, RN, Jeanne Corrao, RN, MS.

Baylor College of Medicine, Houston, Texas. *Principal Investigator*, Neal S. Kleiman, MD; *Research Coordinators*, Kathleen Trainor, RN, Dale Rose, BS, Susan Johnson, RN.

Washington Hospital Center, Washington, D.C. *Principal Investigator*, Jeffrey J. Popma, MD; *Research Coordinator*, Leslie Sweet, RN.

University of Texas Health Science Center at Houston, Houston, Texas. *Principal Investigator*, James T. Willerson, MD; *Research Coordinator*, Lynette Weigelt, RN.

St. Louis University Medical Center, St. Louis, Missouri. *Principal Investigator*, Bernard Chaitman, MD, *Coinvestigator*, Frank Aguirre, MD; *Research Coordinator*, Glenda Haas, RN.

University of Maryland Hospital, Baltimore, Maryland. *Principal Investigator*, Samuel Rodriguez, MD; *Coinvestigator*, Andrew Ziskind, MD, Paul Gurbel, MD; *Research Coordinator*, Cyndi Lemmon, RN, MS.

Heart Institute of Nevada, Las Vegas, Nevada. *Principal Investigator*, Leo Spizzirello, MD; *Coinvestigator*, Matthew McMahon, DO, Harry Thomas, MD, David Navratil, MD; *Research Coordinators*, Jill Lysgaard, RN, Kathy Wilson, RN.

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